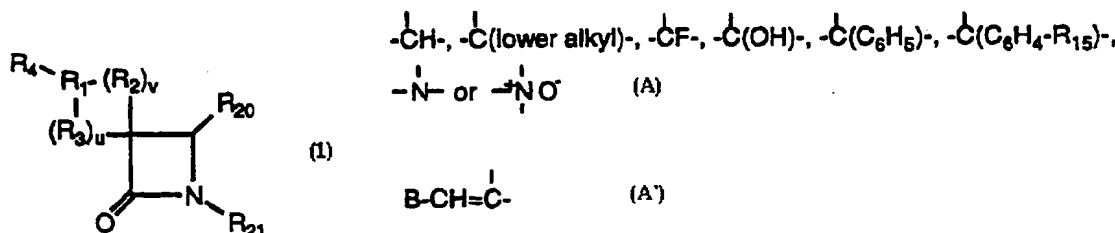




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(54) Title: SPIROCYCLOALKYL-SUBSTITUTED AZETIDINONES USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

**(57) Abstract**

Novel compounds of formula (1) or a pharmaceutically acceptable salt thereof, wherein R₁ is (A); R₂ and R₃ are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)-, -C(di-lower alkyl)-, -CH=CH- and -C(lower alkyl)=CH-; or R₁ together with an adjacent R₂, or R₁ together with an adjacent R₃, form a -CH=CH- or a -CH=C(lower alkyl)- group; u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R₂ is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R₃ is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, the R₂'s can be the same or different; and provided that when u is 2 or 3, the R₃'s can be the same or different; R₄ is B-(CH₂)_mC(O)-, wherein m is 0-5; B-(CH₂)_q-, wherein q is 0-6; B-(CH₂)_e-Z-(CH₂)_r-, wherein Z is -O-, -C(O)-, phenylene, -N(R₈)- or -S(O)₀₋₂-, e is 0-5 and r is 0-5, provided that the sum of e and r is 0-6; B-(C₂-C₆ alkenylene)-; B'-(C₄-C₆ alkadienylene)-; B-(CH₂)_t-Z-(C₂-C₆ alkenylene)-, wherein t is 0-3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2-6; B-(CH₂)_f-V-(CH₂)_g-, wherein V is C₃-C₆ cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; B-(CH₂)_t-V-(C₂-C₆ alkenylene)- or B'-(C₂-C₆ alkenylene)-V-(CH₂)_r-, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6; B-(CH₂)_a-Z-(CH₂)_b-V-(CH₂)_d-, wherein a, b and d are independently 0-6, provided that the sum of a, b and d is 0-6; T-(CH₂)_s-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0-6; or R₁ and R₄ together form the group (A'); B is optionally-substituted phenyl, indanyl, indenyl, naphthyl, tetrahydronaphthyl or optionally substituted-heteroaryl; and R₂₀ and R₂₁ are independently optionally-substituted phenyl, optionally-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, optionally-substituted heteroaryl, optionally-substituted benzofused heteroaryl or cyclopropyl are disclosed, as well as pharmaceutical compositions comprising said compounds, the use of said compounds as hypocholesterolemic agents, processes for preparing the compounds, and the use of said compounds in combination with cholesterol biosynthesis inhibitors to treat or prevent atherosclerosis.

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**SPIROCYCLOALKYL-SUBSTITUTED AZETIDINONES USEFUL
AS HYPOCHOLESTEROLEMIC AGENTS**

BACKGROUND OF THE INVENTION

10 The present invention relates to spirocycloalkyl-substituted azetidinones useful as hypocholesterolemic agents in the treatment and prevention of atherosclerosis, and to the combination of a spirocycloalkyl-substituted azetidinone of this invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis.

15 Atherosclerotic coronary heart disease represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male sex, cigarette smoke and serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is
20 associated with significant elevation of risk.

 Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a key step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester
25 formation and reduction of serum cholesterol is likely to inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

 A few azetidinones have been reported as being useful in
30 lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. 4,983,597 discloses N-sulfonyl-2-azetidinones as anticholesterolemic agents and Ram, et al., in Indian J Chem., Sect. B, 29B, 12 (1990), p. 1134-7, disclose ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates as hypolipidemic agents.

35 European Patent Application 337,549 discloses elastase inhibitory substituted azetidinones comprising a spirocyclo substituent at the 3-position; elastase inhibitors are said to be useful in treating inflammatory conditions resulting in tissue destruction which are associated with various disease states, e.g. atherosclerosis.

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PCT/US92/05972, filed July 21, 1992, and published as WO93/02048 on February 4, 1993 discloses β -lactam (i.e., azetidinone) cholesterol absorption inhibitors which lack a spirocycloalkyl group at the 3-position.

5 In addition to regulation of dietary cholesterol, the regulation of whole-body cholesterol homeostasis in humans and animals involves modulation of cholesterol biosynthesis, bile acid biosynthesis, and the catabolism of the cholesterol-containing plasma lipoproteins. The liver is the major organ responsible for cholesterol biosynthesis and catabolism
10 and, for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density lipoproteins (LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration
15 is correlated with increased atherosclerosis.

When cholesterol absorption in the intestines is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is a decreased hepatic lipoprotein (VLDL) production and an increase in the hepatic clearance of plasma
20 cholesterol, mostly as LDL. Thus, the net effect of an inhibition of intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

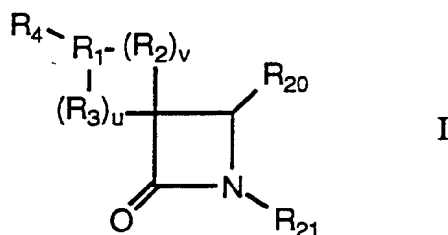
The inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A reductase (EC1.1.1.34) inhibitors has been shown to be an effective way to reduce plasma cholesterol (Witzum,
25 *Circulation*, 80, 5 (1989), p. 1101-1114) and reduce atherosclerosis. Combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy (Illingworth, *Drugs*, 36 (Suppl. 3) (1988), p. 63-71).

30

SUMMARY OF THE INVENTION

Novel hypocholesterolemic compounds of the present invention are represented by the formula I

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or a pharmaceutically acceptable salt thereof, wherein:

R_1 is

$-\overset{|}{\text{CH}}-$, $-\overset{|}{\text{C}}(\text{lower alkyl})-$, $-\overset{|}{\text{CF}}-$, $-\overset{|}{\text{C}}(\text{OH})-$, $-\overset{|}{\text{C}}(\text{C}_6\text{H}_5)-$, $-\overset{|}{\text{C}}(\text{C}_6\text{H}_4\text{-}R_{15})-$,
 $-\overset{|}{\text{N}}-$ or $-\overset{|}{\text{N}}\text{O}^-$;

R_2 and R_3 are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$, $-\text{C}(\text{di-lower alkyl})-$, $-\text{CH}=\text{CH}-$ and $-\text{C}(\text{lower alkyl})=\text{CH}-$; or R_1 together with an adjacent R_2 , or R_1 together with an adjacent R_3 , form a $-\text{CH}=\text{CH}-$ or a $-\text{CH}=\text{C}(\text{lower alkyl})-$ group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R_2 is $-\text{CH}=\text{CH}-$ or $-\text{C}(\text{lower alkyl})=\text{CH}-$, v is 1; provided that when R_3 is $-\text{CH}=\text{CH}-$ or $-\text{C}(\text{lower alkyl})=\text{CH}-$, u is 1; provided that when v is 2 or 3, the R_2 's can be the same or different; and provided that when u is 2 or 3, the R_3 's can be the same or different;

R_4 is $\text{B}-(\text{CH}_2)_m\text{C}(\text{O})-$, wherein m is 0, 1, 2, 3, 4 or 5;

$\text{B}-(\text{CH}_2)_q-$, wherein q is 0, 1, 2, 3, 4, 5 or 6;

$\text{B}-(\text{CH}_2)_e\text{-Z}-(\text{CH}_2)_r-$, wherein Z is $-\text{O}-$, $-\text{C}(\text{O})-$, phenylene, $-\text{N}(\text{R}_8)-$ or $-\text{S}(\text{O})_{0-2}-$, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6;

$\text{B}-(\text{C}_2\text{-C}_6 \text{ alkenylene})-$; $\text{B}'-(\text{C}_4\text{-C}_6 \text{ alkadienylene})-$;

$\text{B}-(\text{CH}_2)_t\text{-Z}-(\text{C}_2\text{-C}_6 \text{ alkenylene})-$, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

$\text{B}-(\text{CH}_2)_f\text{-V}-(\text{CH}_2)_g-$, wherein V is $\text{C}_3\text{-C}_6$ cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

$\text{B}-(\text{CH}_2)_t\text{-V}-(\text{C}_2\text{-C}_6 \text{ alkenylene})-$ or $\text{B}'-(\text{C}_2\text{-C}_6 \text{ alkenylene})\text{-V}-(\text{CH}_2)_t-$, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

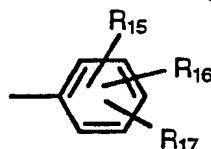
$\text{B}-(\text{CH}_2)_a\text{-Z}-(\text{CH}_2)_b\text{-V}-(\text{CH}_2)_d-$, wherein Z and V are as defined above and a , b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a , b and d is 0, 1, 2, 3, 4, 5 or 6;

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T-(CH₂)_s-, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R₁ and R₄ together form the group $\text{B}-\overset{\overset{|}{\text{I}}}{\text{CH}=\text{C}}-$;

- B is indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or
 5 W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



- 10 W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, -CF₃, -OCF₃, benzyl, R₇-benzyl, benzyloxy, R₇-benzyloxy, phenoxy, R₇-phenoxy,
 15 dioxolanyl, NO₂, -N(R₈)(R₉), N(R₈)(R₉)-lower alkylene-, N(R₈)(R₉)-lower alkylenyloxy-, OH, halogeno, -CN, -N₃, -NHC(O)OR₁₀, -NHC(O)R₁₀, R₁₁O₂SNH-, (R₁₁O₂S)₂N-, -S(O)₂NH₂, -S(O)₀₋₂R₈, tert-butyldimethylsilyloxymethyl, -C(O)R₁₂, -COOR₁₉, -CON(R₈)(R₉), -CH=CHC(O)R₁₂, -lower alkylene-C(O)R₁₂, R₁₀C(O)(lower alkylenyloxy)-,
 20 N(R₈)(R₉)C(O)(lower alkylenyloxy)- and $-\text{CH}_2-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{ } \end{array} \text{R}_{13}$ for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OR₁₀, -C(O)R₁₀, OH, N(R₈)(R₉)-lower alkylene-, N(R₈)(R₉)-lower alkylenyloxy-, -S(O)₂NH₂ and 2-(trimethylsilyl)-
 25 ethoxymethyl;

R₇ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO₂, -N(R₈)(R₉), OH or halogeno;

- R₈ and R₉ are independently H or lower alkyl;
 30 R₁₀ is lower alkyl, phenyl, R₇-phenyl, benzyl or R₇-benzyl;
 R₁₁ is OH, lower alkyl, phenyl, benzyl, R₇-phenyl or R₇-benzyl;
 R₁₂ is H, OH, alkoxy, phenoxy, benzyloxy, $-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{ } \end{array} \text{R}_{13}$

-N(R₈)(R₉), lower alkyl, phenyl or R₇-phenyl;

- 5 -

R_{13} is -O-, -CH₂-, -NH-, -N(lower alkyl)- or -NC(O) R_{19} ;

- R_{15} , R_{16} and R_{17} are independently selected from the group consisting of H and the groups defined for W; or R_{15} is hydrogen and R_{16} and R_{17} , together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R_{19} is H, lower alkyl, phenyl or phenyl lower alkyl; and

- R_{20} and R_{21} are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

- One group of preferred compounds of formula I is that wherein R_{21} is phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl, wherein W is lower alkyl, lower alkoxy, OH, halogeno, -N(R_8)(R_9), -NHC(O)OR₁₀, -NHC(O) R_{10} , NO₂, -CN, -N₃, -SH, -S(O)₀₋₂-(lower alkyl), -COOR₁₉, -CON(R_8)(R_9), -COR₁₂, phenoxy, benzyloxy, -OCF₃, -CH=C(O) R_{12} or tert-butyldimethylsilyloxy, wherein R_8 , R_9 , R_{10} , R_{12} and R_{19} are as defined for formula I. When W is 2 or 3 substituents, the substituents can be the same or different.

- Another group of preferred compounds of formula I is that wherein R_{20} is phenyl or W-substituted phenyl, wherein preferred meanings of W are as defined above for preferred definitions of R_{21} .

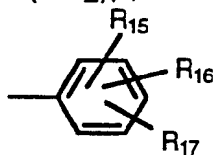
- More preferred are compounds of formula I wherein R_{20} is phenyl or W-substituted phenyl and R_{21} is phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl; W is lower alkyl, lower alkoxy, OH, halogeno, -N(R_8)(R_9), -NHC(O)OR₁₀, -NHC(O) R_{10} , NO₂, -CN, -N₃, -SH, -S(O)₀₋₂-(lower alkyl), -COOR₁₉, -CON(R_8)(R_9), -COR₁₂, phenoxy, benzyloxy, -CH=CHC(O) R_{12} , -OCF₃ or tert-butyl-dimethyl-silyloxy, wherein when W is 2 or 3 substituents, the substituents can be the same or different, and wherein R_8 , R_9 , R_{10} , R_{12} and R_{19} are as defined in formula I.

Also preferred are compounds of formula I wherein R_1 is

$\overset{|}{\text{CH-}}$ or $\overset{|}{\text{C(OH)-}}$. Another group of preferred compounds of formula I is

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that wherein R_2 and R_3 are each $-\text{CH}_2-$ and the sum of u and v is 2, 3 or 4, with $u=v=2$ being more preferred. R_4 is preferably $\text{B}-(\text{CH}_2)_q-$ or $\text{B}-(\text{CH}_2)_e-\text{Z}-(\text{CH}_2)_r$, wherein B , Z , q , e and r are as defined above. B is preferably



- wherein R_{16} and R_{17} are each hydrogen and wherein R_{15} is preferably H, OH, lower alkoxy, especially methoxy, or halogeno, especially chloro. A preferred definition of Z is $-\text{O}-$, e is preferably 0, and r is preferably 0. A preferred definition of q is 0-2. R_{20} is preferably phenyl or W -substituted phenyl. Preferred W substituents for R_{20} are lower alkoxy, especially methoxy and ethoxy, OH, and $-\text{C}(\text{O})\text{R}_{12}$, wherein R_{12} is preferably lower alkoxy. Preferred definitions for R_{21} are phenyl, lower alkoxy-substituted phenyl and F-phenyl.

- Especially preferred are compounds of formula I wherein R_1 is $-\overset{|}{\text{C}}\text{H}-$, or $-\overset{|}{\text{C}}(\text{OH})-$, R_2 and R_3 are each $-\text{CH}_2-$, $u=v=2$, R_4 is $\text{B}-(\text{CH}_2)_q-$, wherein B is phenyl or phenyl substituted by lower alkoxy or chloro, q is 0-2, R_{20} is phenyl, OH-phenyl, lower alkoxy-substituted phenyl or lower alkoxycarbonyl-substituted phenyl, and R_{21} is phenyl, lower alkoxy-substituted phenyl or F-phenyl.

- This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

- In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

- The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor of this invention and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for

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combined use with a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels

- In yet another aspect, the invention relates to a
- 5 pharmaceutical composition comprising an effective amount of a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one
- 10 container an effective amount of a spirocycloalkyl-substituted azetidinone cholesterol absorption inhibitor in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION:

- 15 As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms and "lower alkoxy" similarly refers to alkoxy groups having 1 to 6 carbon atoms.

- "Alkenyl" means straight or branched carbon chains having one or more double bonds in the chain, conjugated or unconjugated, and
- 20 alkadienyl refers to chains having two double bonds in the chain.

Where an alkyl or alkenyl chain joins two other variables and is therefore bivalent, the terms alkylene and alkenylene are used.

- "Cycloalkyl" means a saturated carbon ring of 3 to 6 carbon atoms, while "cycloalkylene" refers to a corresponding bivalent ring,
- 25 wherein the points of attachment to other groups include all positional isomers.

"Halogeno" refers to fluorine, chlorine, bromine or iodine radicals.

- "Heteroaryl" includes all positional isomers for a given
- 30 heteroaryl group as defined above, for example 2-pyridyl, 3-pyridyl and 4-pyridyl. Benzofused heteroaryl refers to radicals formed by the bonding of a benzene radical to adjacent carbon atoms on a heteroaryl ring; examples are indolyl, quinolyl, quinazolinyl, quinoxalinyl, benzotriazolyl, indazolyl, benzoxazolyl, benzothienyl and benzofuranyl.

- 35 "Phenylene" means a bivalent phenyl group, including ortho, meta and para-substitution.

"(Lower alkoxyimino)lower alkyl" refers to the group (C₁-C₆ lower alkoxy)-N=CH-(C₁-C₅ lower alkyl). "Lower alkanedioyl" means

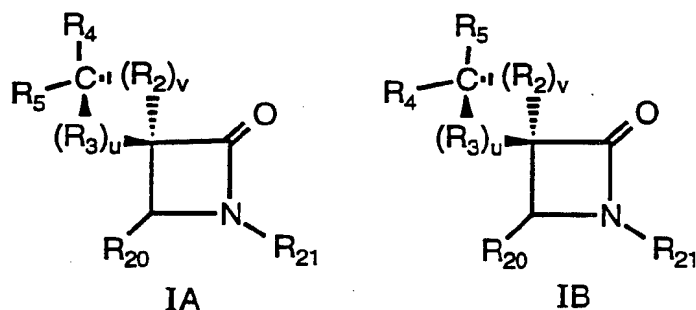
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radicals of the formula $-\text{OC}(\text{O})(\text{CH}_2)_{1-4}\text{C}(\text{O})\text{OH}$, while "lower alkyl lower alkanedioyl" means radicals of the formula $-\text{OC}(\text{O})(\text{CH}_2)_{1-4}\text{C}(\text{O})\text{O}-(\text{lower alkyl})$.

5 R_7 -benzyl and R_7 -benzyloxy refer to benzyl and benzyloxy radicals which are substituted on the phenyl ring.

Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including diastereomers and rotational isomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

15 For compounds of the invention wherein R_1 is not N, at least two diastereomeric forms are possible. The following formulae IA and IB represent structures designated herein as "diastereomer A", wherein the lactam carbonyl group and the R_4 group are SYN, and "diastereomer B", wherein the lactam carbonyl group and the R_4 group are ANTI, respectively:



wherein R_5 is hydrogen, lower alkyl, fluoro, hydroxy, phenyl, or R_{15} -substituted phenyl, and R_2 , R_3 , R_4 , R_{15} , R_{20} , R_{21} , u and v are as defined above.

25 Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids.

30 Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids

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well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium

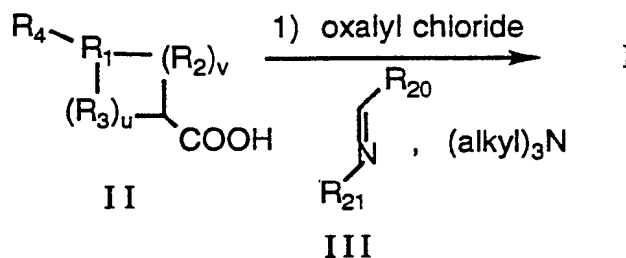
- 5 bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base forms for purposes of the invention.

- Certain compounds of the invention are acidic (e.g., those
10 compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines,
15 N-methylglucamine and the like.

- Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin and CI-981; HMG CoA synthetase inhibitors, for example L-659,699 ((E,E-11-[3'R-(hydroxy-
20 methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalastatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride). Preferred HMG CoA reductase inhibitors are lovastatin,
25 pravastatin and simvastatin.

Compounds of formula I, wherein R_1 , R_2 , R_3 , R_4 , R_{20} , R_{21} , u and v are as defined above, can be prepared by known methods as shown in the following processes A to F.

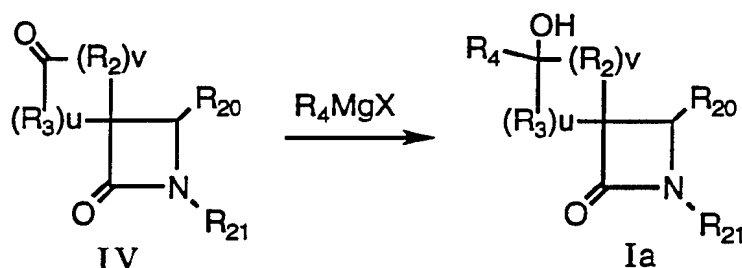
30 Process A:



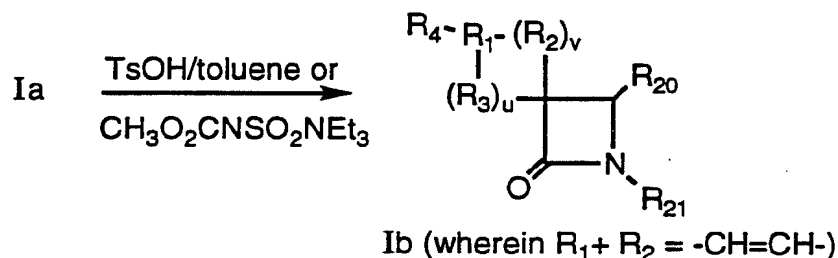
A carboxylic acid of formula II can be converted to the corresponding acid chloride by refluxing with a reagent such as oxalyl

- 10 -

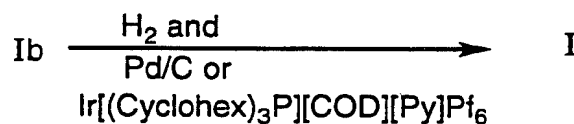
- chloride in an inert solvent such as CH_2Cl_2 . The acid chloride is then refluxed with an imine of formula III in an inert solvent such as CH_2Cl_2 , heptane or toluene, in the presence of a trialkylamine (i.e., $(\text{alkyl})_3\text{N}$) such as triethylamine, tributylamine or diisopropylethylamine. Generally, all possible diastereomers of formula I are produced by this process.

Process B:

- A keto-azetidinone of formula IV can be converted to a carbinol of formula Ia, i.e., a compound of formula I wherein R_1 is $\text{-}\overset{\text{I}}{\text{C}}(\text{OH})\text{-}$, by treatment with a Grignard reagent of formula R_4MgX , wherein R_4 is as defined above and X is a halogen such as bromine, chlorine or iodine.

Process C:

- A carbinol of formula Ia is converted to an olefin of formula Ib, wherein R_1 and an adjacent R_2 form a double bond (other R_2 groups can also be present) by dehydration with a mild acid such as p-toluenesulfonic acid (p-TsOH) under anhydrous conditions, e.g., using toluene as a solvent, or by treatment with a dehydrating agent such as (methoxycarbonylsulfamoyl)-triethylammonium hydroxide inner salt.

Process D:

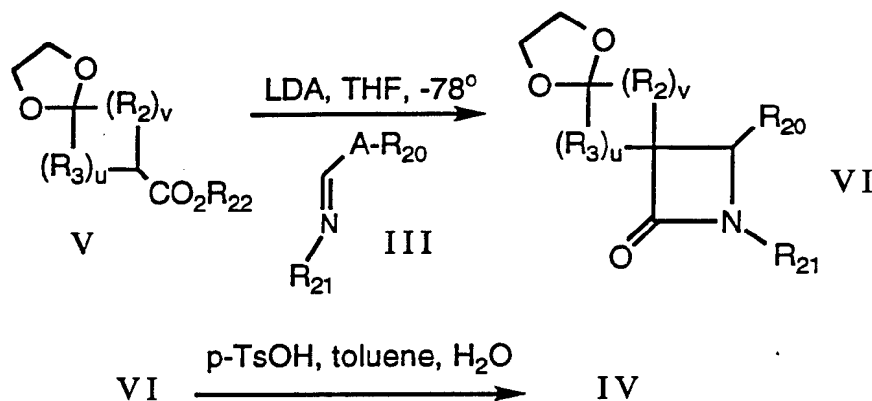
An olefin of formula Ib is reduced with hydrogen in the presence of a suitable catalyst such as palladium or an iridium salt to

- 11 -

obtain the desired azetidinone of formula I. When the iridium salt is used, the resulting products have primarily the ANTI stereochemistry, IB.

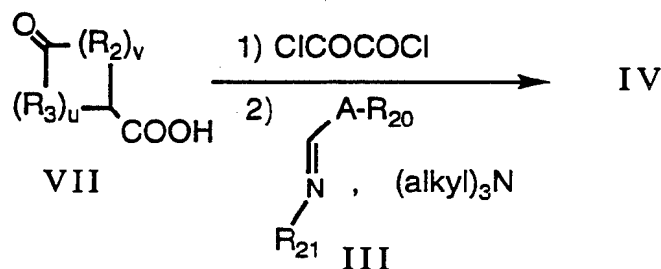
- 5 Keto-azetidinone starting materials of formula IV can be prepared, for example, by the following processes:

Process E:



- A carboxylic acid ester of formula V, wherein R₂₂ is lower alkyl, such as ethyl, or a chiral moiety such as menthyl or 10-(diisopropyl-sulfonamido)-isobornyl, is treated with a strong base such as lithium diisopropylamide (LDA) in a suitable solvent such as tetrahydrofuran (THF) at -78°C. An imine of formula III is added and the reaction mixture is stirred at -78°C for a suitable period, e.g., one hour, then allowed to warm to room temperature. The product of formula VI is isolated using conventional purification techniques. When the ester group R₂₂ is chiral, the product is non-racemic. The ketal protecting group is removed by treatment with a mild acid such as p-TsOH to obtain the keto-azetidinone of formula IV.

Process F:



A ketoacid of formula VII can be treated with ClCOCOCI and reacted with an imine of formula III as described in Process A to obtain a keto-azetidinone of formula IV.

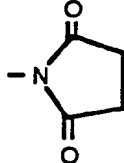
- 12 -

The carboxylic acids and imines of formulas II, III, V and VII used as starting materials in the above process are known in the art or can be prepared by one skilled in the art using well known procedures. Typical procedures for preparing a variety of carboxylic acids are

5 described below in Preparations 1 to 6.

Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 3 shows some typical protecting groups:

10

| Group to be Protected | Table 3 Group to be Protected and Protecting Group |
|-----------------------|--|
| -COOH | -COOalkyl, -COObenzyl, -COOphenyl |
| >NH | $\text{>NCOalkyl, >NCObenzyl, >NCOphenyl,}$ $\text{>NCH}_2\text{OCH}_2\text{CH}_2\text{Si(CH}_3)_3,$ $\text{NC(O)OC(CH}_3)_3,$ $\text{>N-benzyl, >NSi(CH}_3)_3,$ $\text{>NSi(CH}_3)_2\text{C(CH}_3)_3$ |
| -NH ₂ |  |
| -OH | $\text{-OCH}_3, \text{-OSi(CH}_3)_3, \text{-OSi(CH}_3)_2\text{C(CH}_3)_3, \text{-OC(O)alkyl}$ |

We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesteryl esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the esterification and/or intestinal absorption of cholesterol; they are, therefore, useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

15

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The *in vivo* activity of the compounds of formula I can be determined by the following procedure:

- 13 -

In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by IM injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesteremic dose of a compound of formula I is about 7 to about 30 mg/kg of body weight per day. For an average body weight of 70kg, the dosage level is therefore from about 500 to about 2000 mg of drug per day, given in a single dose or 2-4 divided doses.

The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Following are examples of preparing carboxylic acid starting materials and novel compounds of formula I. The stereochemistry listed is relative stereochemistry unless otherwise noted.

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Preparation 1**4-Phenyl-cyclohexanecarboxylic acid**

- STEP 1: Cool a mixture of 4-phenyl-cyclohexanone (30 g) and tosylmethyl isocyanide (36.9 g) in dimethoxyethane (800 mL) in an ice/acetone bath. Add a solution of potassium t-butoxide (38.7 g) in dimethoxyethane (300 mL) and t-butanol (300 mL). Stir the reaction mixture for 4h, pour into water and extract the product with ethyl acetate (EtOAc). Separate the organic layer, concentrate and use in STEP 2 without purification.
- STEP 2: Dissolve the product from STEP 1 (32.8 g) in CH₃OH (240 mL) and add water (800 mL), Ba(OH)₂ (95 g) and NaOH (7.8 g). Heat the reaction mixture at reflux for 24h. Remove most of the CH₃OH under vacuum and extract the aqueous solution with ether (Et₂O). Separate the aqueous layer, acidify with conc. HCl and extract the product with Et₂O. Concentrate the ether solution to obtain the title compound (17.6 g).
- 4-Phenyl-4-methyl-cyclohexanecarboxylic acid is similarly prepared from 4-phenyl-4-methyl-cyclohexanone.

Preparation 2**4-(4-Chlorophenyl)-cyclohexanecarboxylic acid**

- STEP 1: Slowly add 4-chlorophenylmagnesium chloride (5.9 mL of 1M solution) to a solution of ethyl 4-oxo-cyclohexanecarboxylate (1.0 g) in Et₂O at 0°C. After 1h, pour the reaction mixture into 1N HCl and extract with Et₂O. Separate the organic layer, wash with water, brine and concentrate to give ethyl 4-(4-chlorophenyl)-4-hydroxy-cyclohexanecarboxylate (1.75 g) which is used without purification in the next step.
- STEP 2: Dissolve the product (1.75 g) from STEP 1 in THF (100 mL), treat with 40% H₂SO₄ (25 mL) and heat the reaction mixture at reflux for 5.5h. Remove most of the solvent in vacuo, dilute the reaction mixture with water and extract with Et₂O. Separate the organic layer and concentrate to give 4-(4-chlorophenyl)-cyclohex-3-enecarboxylic acid (1.36 g).
- STEP 3: Reduce a solution of the product of STEP 2 (1.36 g) in EtOAc (50 mL) over 10% Pd/C under H₂ (50 psi) for 14 h. Filter the catalyst and concentrate the solution to give the title compound (1.36 g).
- 4-(4-Methoxyphenyl)-cyclohexanecarboxylic acid is similarly prepared.

- 15 -

Preparation 34-Cyclohexyl-cyclohexanecarboxylic acid

Reduce a solution of 4-biphenylcarboxylic acid (10 g) in ethanol (EtOH) (175 mL) and EtOAc (30 mL) over 5% rhodium/alumina (7 g) under H₂ (60 psi) for 8 days. Filter the catalyst and concentrate the solution to obtain the title compound (9.92 g).

Preparation 44-Benzyl-cyclohexanecarboxylic acid

STEP 1: Reduce a solution of terphthalic acid mono-methyl ester (12.6 g) using a procedure similar to that of Preparation 3 to obtain 1,4-cyclohexanedicarboxylic acid mono-methyl ester (12.64 g). The crude product is used without purification in the next step.

STEP 2: Add ClCOCOCl (4.1 g) to a solution of the product of STEP 1 (3.0 g) in CH₂Cl₂ (15 mL) and heat the mixture at reflux for 1.5h. Remove excess ClCOCOCl in vacuo and dissolve the product in benzene. Cool the reaction mixture in an ice/water bath and slowly add AlCl₃ (4.74 g). Stir the reaction mixture overnight as it warms to ambient temperature and pour into a conc. HCl/ice mixture. Extract the product with Et₂O, separate the organic layer, wash with water and brine, then concentrate to obtain methyl 4-(4-benzoyl)-cyclohexane-carboxylate (3.9 g).

STEP 3: Reduce a solution of the product of STEP 2 (2.5 g) in EtOAc (15 mL) and acetic acid (HOAc) (50 mL) over 10%Pd/C (0.3 g) under H₂ (60 psi) for 22h. Filter the catalyst, dilute the reaction mixture with water and extract the product with Et₂O. Separate the organic layer and concentrate to obtain a mixture of methyl 4-(α -hydroxybenzyl)-cyclohexanecarboxylate and methyl (4-benzyl)cyclohexane-carboxylate (2.46 g).

STEP 4: Dissolve the product from STEP 3 (2.46 g) in THF (100 mL), treat with 40% H₂SO₄ (25 mL) and heat the reaction mixture at reflux for 5 h. Pour the reaction mixture into excess water and extract with EtOAc. Separate the organic layer, concentrate, and reduce the crude mixture over 10%Pd/C (0.25 g) under H₂ (60 psi) overnight. Filter the catalyst and concentrate the solution to obtain the title compound (2.42 g).

Preparation 54-(2-Phenylethyl)-cyclohexanecarboxylic acid

STEP 1: Slowly add 2-phenylethyl bromide (2.6 g) to a slurry of Mg (0.37 g) in THF (50 mL) and heat at reflux for 4h. Cool the solution to ambient temperature and add to a solution of ethyl 4-oxo-cyclo-hexane-carboxylate (2.4 g) in THF (50 mL). After 2h, pour the reaction mixture into

- 16 -

- a half-saturated solution of NH_4Cl and extract with EtOAc. Partially purify the product on a silica gel column, eluting with EtOAc. Dissolve the product in toluene (100 mL), treat with p-TsOH and heat at reflux overnight with azeotropic removal of water. Cool the reaction mixture,
- 5 wash with saturated NaHCO_3 solution and concentrate. Purify the crude product on a silica gel column, eluting with CH_2Cl_2 to obtain ethyl 4-(2-phenylethyl)-cyclohex-3-enecarboxylate (0.45 g) and 1-(2-phenyl-ethyl)-2-oxabicyclo[2.2.2]octan-3-one (0.71 g). Dissolve 1-(2-phenyl-ethyl)-2-oxabicyclo[2.2.2]octan-3-one in EtOH, treat with conc.HCl (catalytic) and
- 10 heat at reflux overnight. Dilute the reaction mixture with water and extract with EtOAc. Concentrate the organic layer to obtain additional ethyl 4-(2-phenylethyl)-cyclohex-3-enecarboxylate (0.88 g).
- STEP 2: To a solution of the product of STEP 1 (1.33 g) in EtOAc (40 mL), add 10% Pd/C (0.2 g) and hydrogenate overnight at 58 psi. Filter the
- 15 catalyst and concentrate the reaction mixture to give ethyl 4-(2-phenylethyl)-cyclohexanecarboxylate (1.26 g).
- STEP 3: To a solution of the product of STEP 2 (1.26 g) in MeOH (20 mL), add water (5 mL) and LiOH (0.61 g) and stir overnight at ambient temperature. Dilute the reaction mixture with water and extract with Et_2O .
- 20 Acidify the aqueous layer with conc.HCl and extract with EtOAc. Separate the organic layer, wash with water and brine, and concentrate to obtain the title compound (1.06 g).

Preparation 6

3-Benzyl-cyclobutanecarboxylic acid

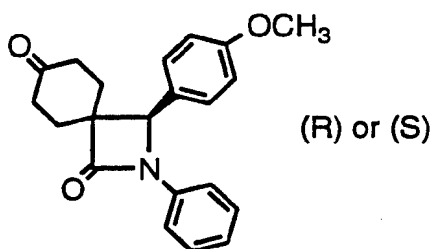
- 25 STEP 1: Slowly add a solution of diethyl 2-benzylmalonate (20 g) in Et_2O (300 mL) to a slurry of LiAlH_4 (6 g) in Et_2O (300 mL), then heat the reaction mixture at reflux for 14h. Carefully add 4N NaOH to the reaction mixture until there is no precipitate, then extract with EtOAc. Concentrate the organic layer and purify the crude product on a silica gel column,
- 30 eluting with EtOAc to obtain 2-benzyl-1,3-propanediol (8.45 g).
- STEP 2: Slowly add $(\text{C}_6\text{H}_5)_3\text{P}$ (17.4 g) to a solution of the product of STEP 1 (5 g) in CH_2Cl_2 (200 mL) containing CBr_4 (21 g) at 0°C . Stir the reaction mixture overnight and allow to warm to ambient temperature. Evaporate the solvent in vacuo, triturate the crude product with pentane,
- 35 filter, concentrate the filtrate and purify the residue on a silica gel column, eluting with hexane to give 2-benzyl-1,3-propanedibromide (5.47 g).
- STEP 3: Add diethyl malonate (3 g) to a slurry of NaH (0.514 g) in dimethylformamide (DMF) (75 mL) at ambient temperature. After 1 h, heat

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- the reaction mixture to 100°C for 1h, cool to ambient temperature, add a solution of the product of STEP 2 (5 g) in DMF (25 mL) and stir at ambient temperature for 2.5h, followed by 2h at 150°C. Cool the mixture to ambient temperature, add NaH (0.514 g) and after 30 min., heat at 150°C
- 5 overnight. Cool the reaction mixture, pour into excess water and extract with EtOAc. Separate the organic layer, wash with water and concentrate. Purify the crude product on a silica gel column, eluting with EtOAc:hexane (1:9) to obtain diethyl (3-benzyl)-cyclobutyl-1,1-dicarboxylate (3 g).
- STEP 4: To a solution of the product of STEP 3 (3 g) in EtOH (20 mL),
- 10 add water (5 mL) and KOH (2.9 g) and heat at reflux overnight. Dilute the reaction mixture with water and extract with Et₂O. Acidify the aqueous layer with conc.HCl and extract with CH₂Cl₂. Separate the organic layer and concentrate to give 3-benzyl-cyclobutyl-1,1-dicarboxylic acid (2.31 g).
- STEP 5: Heat the product of STEP 4 (2.31 g) at 170-180°C under
- 15 vacuum (60-70 mm) for 1.5h to obtain the title compound (1.85 g).

In a similar manner, 2-(2-phenylethyl)malonate is converted to 2-(2-phenylethyl)cyclobutanecarboxylic acid.

Preparation 7



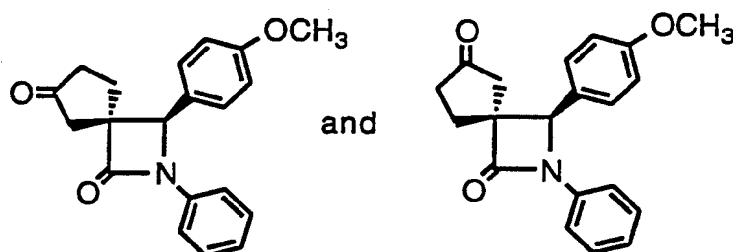
- 20 STEP 1: Heat a mixture of 4-carbomethoxycyclohexanone (4.4 g, 0.028 moles), HOCH₂CH₂OH (3.2 mL, 0.056 moles), and a catalytic amount of p-TsOH in toluene at reflux for 4 hr with continuous removal of water. Cool to room temperature, wash the organic layer with water, dry over MgSO₄, and evaporate to give the crude ketal. Dissolve ketal in MeOH (80 mL)
- 25 containing KOH (5.6 g) and stir at room temperature overnight. Concentrate to dryness and dissolve in Et₂O (100 mL). Adjust to pH 2 with 1N HCl. Extract with Et₂O (3 x 100 mL), dry over MgSO₄ and evaporate to obtain 4.0 grams of the ethylene ketal of 4-cyclohexanonecarboxylic acid.
- STEP 2: Add the product from Step 1 (0.344 g, 1.8 mmol) and 10-
- 30 diisopropylsulfonamido)-isoborneol (0.570 g, 1.8 mmol) to a mixture of DCC (0.556 g, 2.7 mmol), dimethylaminopyridine (DMAP) (0.330 g, 2.7 mmol), and DMAP HCl (0.003 g) in CH₂Cl₂ (5 mL). Stir at room temp. overnight, dilute with Et₂O (150 mL) and filter. Concentrate the filtrate

- 18 -

under vacuum and purify the crude ester by chromatography on silica gel, eluting with 30% EtOAc/hexane to obtain 0.508 grams of the ester.

- STEP 3: Prepare a solution of LDA (from $[(\text{CH}_3)_2\text{CH}]_2\text{NH}$ (0.23 mL) and 1.6M $\text{CH}_3(\text{CH}_2)_3\text{Li}$ (1.03 mL) in hexane) in THF (5 mL), cool to -78°C and
- 5 add a solution of the product of Step 2 in THF (5 mL). Stir at -78°C for 1.5 hr, then add a solution of (N-(4-methoxy-benzylidene)aniline (0.278 g, 1.32 mmol) in THF (5 mL). Stir this mixture at -78°C for 1 hr and at room temperature for 1 hr. Quench the reaction with a solution of 10 % aqueous KHSO_4 (20 mL), extract with EtOAc (3x20 mL), dry the organic layers over
- 10 MgSO_4 and evaporate. Purify the crude product by chromatography over silica gel, eluting with 40% EtOAc/hexane to obtain 0.266 g of product.
- STEP 4: Stir the product of Step 3 overnight in 5:1 acetone: 3N HCl to obtain 0.21 grams of the title compound. If 10-diisopropylsulfonamido)-isoborneol derived from (+)-10-camphorsulfonyl chloride is used in Step
- 15 1, the product has the (S)-configuration.

Preparation 8

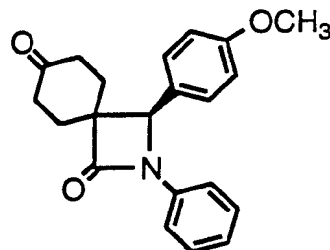


- STEP 1: To a solution of ethyl 3-oxocyclopentanecarboxylate (2.63 g, 0.0169 moles) in benzene (50 mL), add $\text{HOCH}_2\text{CH}_2\text{OH}$ (2.10 g, 0.0338
- 20 moles) and pyridinium tosylate (0.85 g, 0.0034 moles). Heat at reflux with removal of water for 2.5 hr. Remove the solvent under vacuum and take up the residue in Et_2O (100 mL). Wash with saturated Na_2CO_3 and concentrate to a yellow oil. Purify by chromatography on silica gel, eluting with 10 % EtOAc/hexane to obtain 2.92 grams of the ketal ester.
- 25 STEP 2: React the product of Step 1 (0.30 g, 0.0015 moles) with LDA (1.2 equivalents) in THF followed by N-(4-methoxybenzylidene)aniline as described for Preparation 7, Step 3, to obtain 0.52 grams of the resulting azetidinone as a mixture of diastereomers. Separate these diastereomers by chromatography on silica gel, eluting with 20% EtOAc/hexane to obtain
- 30 0.16 grams of component A and 0.22 grams of component B.
- STEP 3: Treat component A of Step 2 (1.38 g) with aqueous HCl as described for Preparation 7, Step 4, to obtain 1.15 grams of rel (3R,4R)-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.4]octane-1,6-dione. Similar

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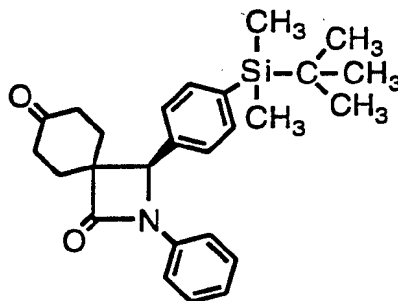
treatment of component B yields rel (3R,4S)-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.4]octane-1,6-dione.

Preparation 9



5 Treat a solution of 4-cyclohexanonecarboxylic acid (4.6 g, 0.0323 moles) in CH_2Cl_2 (50 mL) with ClCOCOCI (5.7 mL, 0.0648 moles) as described in Example 1, below. React the resulting acid chloride with N-(4-methoxybenzylidene)aniline using the procedure described in Example 1 to obtain the title compound (10.03 g).

10 In a similar manner, using N-(4-methoxybenzylidene)-4(t-butyl-dimethylsilyloxy)aniline, prepare:



Examples 1 and 1A

15 2,3-Bis-(4-methoxyphenyl)-7-(4-chlorophenyl)-
 2-azaspiro[3.5]nonan-1-one

 Add ClCOCOCI (1.43 g) to a solution of the product of Preparation 2 (1.34 g) in CH_2Cl_2 (15 mL) and heat at reflux for 2h. Remove the solvent and excess ClCOCOCI under vacuum. Dissolve the resultant acid chloride in CH_2Cl_2 (5 mL), add this solution to N-(4-methoxybenzylidene)anisidine (1.35 g) and triethylamine (Et_3N) (1.25 g) in CH_2Cl_2 (25 mL) and heat at reflux overnight. Pour the reaction mixture into 1N HCl and extract the product with CH_2Cl_2 . Separate the organic layer, wash with saturated NaHCO_3 and concentrate. Purify the crude material on a silica gel column, eluting with CH_2Cl_2 :hexane (95:5) to give:

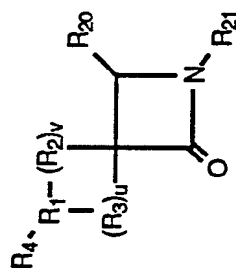
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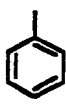

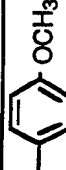
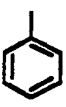
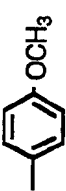

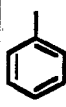
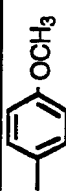
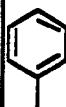
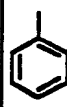
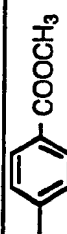
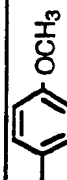
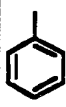
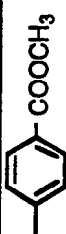


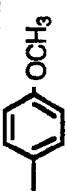




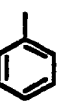
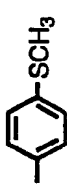

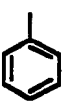
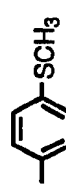

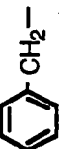
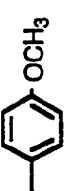

(1) Diastereomer A of the title compound: 0.52 g; m.p. 166-167;
Mass spectrum: Calculated 461 and observed 462;
Elemental analysis: Calculated: C=72.8, H=6.11, N=3.03
Found: C=72.72, H=6.11, N=3.15

5 (1A) Diastereomer B of the title compound: 0.475 g; m.p. 87-89
Mass spectrum: Calculated 461 and observed 462;
Elemental analysis: Calculated: C=72.8, H=6.11, N=3.03
Found: C=72.79, H=6.17, N=3.12.


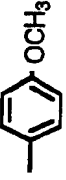





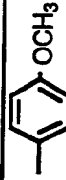
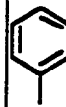

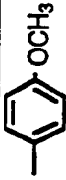

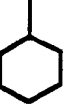
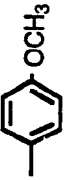

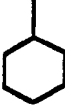
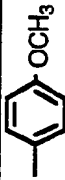

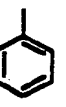
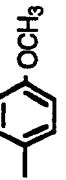

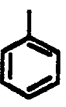
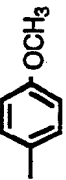

10 Other 2-azaspiro[3.5]nonan-1-ones and 2-azaspiro[3.3]-
heptan-1-ones similarly prepared are shown in the following table:



| Ex. | Dia- ster. | R ₁ | -(R ₂) _v | -(R ₃) _u | R ₄ | R ₂₀ | R ₂₁ | mp, °C | MS | Elem. Anal. |
|-----|---------------|----------------|----------------------------------|----------------------------------|----------------|-----------------|-----------------|-------------|------------------------|--|
| 2 | A | CH | -(CH ₂) ₂ | -(CH ₂) ₂ | | | | 68- 71 | Calcd: 427 Obs: 427 | |
| 3 | B | CH | -(CH ₂) ₂ | -(CH ₂) ₂ | | | | 75- 77 | Calcd: 427 Obs: 427 | Calcd: C: 78.66, H: 6.84, N: 3.28 Found: C: 78.26, H: 6.77, N: 3.36 |
| 4 | A | CH | -(CH ₂) ₂ | -(CH ₂) ₂ | | | | - | Calcd: 397 Obs: 398 | Calcd: C: 81.58, H: 6.85, N: 3.52 Found: C: 81.06, H: 6.76, N: 3.65 |
| 5 | B | CH | -(CH ₂) ₂ | -(CH ₂) ₂ | | | | - | Calcd: 397 Obs: 398 | Calcd: C: 81.58, H: 6.85, N: 3.52 Found: C: 80.87, H: 6.75, N: 3.68 |
| 6 | A | CH | -(CH ₂) ₂ | -(CH ₂) ₂ | | | | - | Calcd: 411 Obs: 412 | Calcd: C: 81.72, H: 7.10, N: 3.40 Found: C: 81.59, H: 7.05, N: 3.60 |
| 7 | B | CH | -(CH ₂) ₂ | -(CH ₂) ₂ | | | | - | Calcd: 411 Obs: 411 | |
| 8 | - | N | -(CH ₂) ₂ | -(CH ₂) ₂ | | | | - | Calcd: 428 Obs: 429 | Calcd: C: 75.68, H: 6.59, N: 6.54 Found: C: 75.40, H: 6.66, N: 6.52 |
| 9 | A | CH | -(CH ₂) ₂ | -(CH ₂) ₂ | | | | 191- 193 | Calcd: 396 Obs: 397 | Calcd: C: 81.58, H: 6.85, N: 3.52 Found: C: 81.57, H: 6.84, N: 3.55 |

| Ex. | Dia-ster. | R ₁ | -(R ₂)v- | -(R ₃)ur- | R ₄ | R ₂₀ | R ₂₁ | mp, C° | MS | Elem. Anal. |
|---------|-----------|---------------------|------------------------------------|------------------------------------|---|---|---|-------------|------------------------|--|
| 10 | B | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | 178- 180 | Calcd: 396 Obs: 397 | Calcd: C: 81.58, H: 6.85, N: 3.52 Found: C: 81.56, H: 6.82, N: 3.56 |
| 11 | A | C(CH ₃) | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | - | Calcd: 411 Obs: 412 | |
| 12 | B | C(CH ₃) | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | - | Calcd: 411 Obs: 412 | |
| 13 | A | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | 184- 185 | Calcd: 455 Obs: 455 | Calcd: C: 76.46, H: 6.42, N: 3.07 Found: C: 76.20, H: 6.38, N: 3.07 |
| 14 | B | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | 125- 127 | Calcd: 455 Obs: 455 | Calcd: C: 76.46, H: 6.42, N: 3.07 Found: C: 76.36, H: 6.72, N: 3.19 |
| 15 | A | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | 149- 150 | Calcd: 427 Obs: 428 | Calcd: C: 78.66, H: 6.84, N: 3.28 Found: C: 78.74, H: 6.89, N: 3.48 |
| 16 | B | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | 161- 162 | Calcd: 427 Obs: 428 | Calcd: C: 78.66, H: 6.84, N: 3.28 Found: C: 78.53, H: 6.80, N: 3.47 |
| 17 A | A | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | - | Calcd: 413 Obs: 414 | - |
| 17 B | B | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | - | Calcd: 413 Obs: 413 | - |
| 18 | A | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | 65- 69 | Calcd: 411 Obs: 412 | HRMS Calcd: 412.2277 Found: 412.2272 |

| Ex. | Diast. | R ₁ | -(R ₂) _n ⁻ | -(R ₃) _m ⁻ | R ₄ | R ₂₀ | R ₂₁ | mp, °C | MS | Elem. Anal. |
|-----|--------|----------------|---|---|----------------|-----------------|-----------------|---------|------------------------|--|
| 19 | B | CH | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 126-130 | Calcd: 411 Obs: 412 | HRMS Calcd: 412.2277 Found: 412.2269 |
| 20 | A | CH | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 167-168 | Calcd: 431 Obs: 432 | Calcd: C: 75.08, H: 6.07, N: 3.24 Found: C: 75.07, H: 6.07, N: 3.31 |
| 21 | B | CH | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 76-78 | Calcd: 431 Obs: 432 | Calcd: C: 75.08, H: 6.07, N: 3.24 Found: C: 75.28, H: 6.04, N: 3.33 |
| 22* | B | CH | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 76-77 | Calcd: 427 Obs: 428 | |
| 23* | B | CH | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 76-77 | Calcd: 427 Obs: 428 | Calcd: C: 78.85, H: 6.62, N: 3.28 Found: C: 78.84, H: 6.65, N: 3.30 |
| 24 | A | CH | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 57-59 | Calcd: 425 Obs: 426 | Calcd: C: 81.85, H: 7.34, N: 3.29 Found: C: 81.97, H: 7.34, N: 3.21 |
| 25 | B | CH | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 53-55 | Calcd: 425 Obs: 426 | Calcd: C: 81.85, H: 7.34, N: 3.29 Found: C: 81.77, H: 7.24, N: 3.29 |
| 26* | B | CH | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 174-175 | Calcd: 414 Obs: 415 | Calcd: C: 78.16, H: 6.07, N: 3.38 Found - C: 78.20, H: 6.10, N: 3.39 |
| 27* | B | CH | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 174-175 | Calcd: 414 Obs: 415 | Calcd: C: 78.16, H: 6.07, N: 3.38 Found: C: 78.17, H: 6.09, N: 3.38 |
| 28 | - | | -(CH ₂) ₂ ⁻ | -(CH ₂) ₂ ⁻ | | | | 163-164 | Calcd: 429 Obs: 430 | Calcd: C: 75.43, H: 5.63, N: 3.26 Found: C: 75.35, H: 5.67, N: 3.35 |

| Ex. | Dia-ster. | R ₁ | -(R ₂)v ⁻ | -(R ₃)u ⁻ | R ₄ | R ₂₀ | R ₂₁ | mp, Co | MS | Elem. Anal. |
|------|-----------|----------------|------------------------------------|------------------------------------|---|---|---|--|------------------------|--|
| 29 A | A | CH | -CH ₂ - | -CH ₂ - |  |  |  | 56-58 | Calcd: 383 Obs: 384 | Calcd: C: 81.43, H: 6.57, N: 3.65 Found: C: 81.54, H: 6.49, N: 3.56 |
| 29 B | B | CH | -CH ₂ - | -CH ₂ - |  |  |  | 97-98 | Calcd: 383 Obs: 384 | Calcd: C: 81.43, H: 6.57, N: 3.65 Found: C: 81.09, H: 6.36, N: 3.42 |
| 30 A | A | CH | -CH ₂ - | -CH ₂ - |  |  |  | ¹ H NMR (400 MHz, CDCl ₃) δ 6.90-7.30(m, 14H), 4.71(s, 1H), 3.82(s, 3H), 2.66(ddd, 1H, J=3.00, 7.73, 11.60), 2.29(ddd, 1H, J=4.20, 7.94, 11.91), 1.94(ddd, 1H, J=9.56, 11.60), 1.23(ddd, 1H, J=8.54, 11.91), 2.46(m, 3H), 1.59(m, 2H) | | |
| 30 B | B | CH | -CH ₂ - | -CH ₂ - |  |  |  | ¹ H NMR (400 MHz, CDCl ₃) δ 6.90-7.32(m, 14H), 4.87(s, 1H), 3.82(s, 3H), 2.42-2.56(m, 3H), 2.95(ddd, 1H, J=7.39, 11.9), 2.05(m 1H), 1.92(ddd, 1H, J=7.63, 12.2), 1.64(ddd, J=8.24, 3.36, 11.9), 1.83(q, 2H, J=7.63) | | |
| 31 | A | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | 180-181 | Calcd: 403 Obs: 404 | Calcd: C: 80.36, H: 8.24, N: 3.47 Found: C: 80.41, H: 8.19, N: 3.57 |
| 32 | B | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | 141-143 | Calcd: 403 Obs: 404 | Calcd: C: 80.36, H: 8.24, N: 3.47 Found: C: 80.35, H: 8.15, N: 3.74 |
| 33 | A | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | - | - | Calcd: C: 79.74, H: 7.53, N: 3.87 Found: C: 79.36, H: 7.57, N: 3.98 |
| 34 | B | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  | - | Calcd: 361 Obs: 361 | - |

* = Single Enantiomers

- 25 -

Enantiomeric compounds of Examples 22 and 23 were prepared by chromatographic resolution of the racemate in a CHIRACEL OD HPLC column eluting with 93:7 hexane:isopropanol at a flow rate of 5 mL/min.

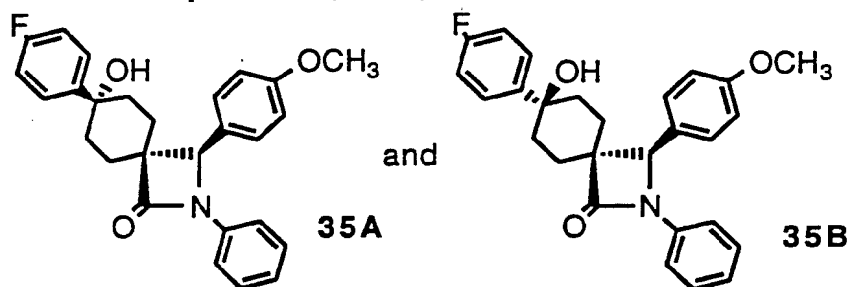
5 Enantiomeric compounds of Examples 26 and 27 were prepared by chromatographic resolution of the racemate in a CHIRACEL OD HPLC column eluting with 95:5 hexane:isopropanol at a flow rate of 5 mL/min.

Example 26: $[\alpha]_D^{25} = +60.7^\circ$ (CH₃OH)

Example 27: $[\alpha]_D^{25} = -58.1^\circ$ (CH₃OH)

10

Examples 35A, 35B, 35C, 35D and 35E

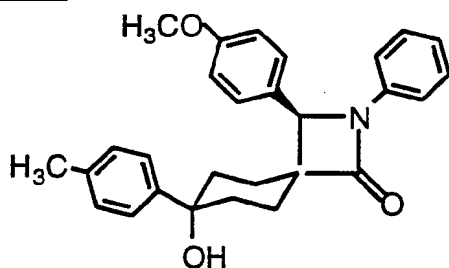


To a solution of the product of Preparation 7 (1.1 g, 3.28 mmol) in Et₂O (20 mL) at 0°C, add a solution of 4-fluorophenylmagnesium bromide (4.9 mL, 4.92 mmol) in THF over 5 min. Stir at 0°C for 1.5 hr, then stir at room temperature for 3 hr. Quench the reaction with sat'd NaHSO₄ and extract with EtOAc (3 x 30 mL). Dry the organic layers over Na₂SO₄ and evaporate the solvent to obtain 1.57 grams of crude product. Purify by chromatography over silica gel, eluting with 95:5 CH₂Cl₂:EtOAc to obtain 0.9 g of the ANTI isomer, mp=168-169°C, and 0.27 g of the SYN isomer.

20

In a similar manner, the following compounds are prepared:

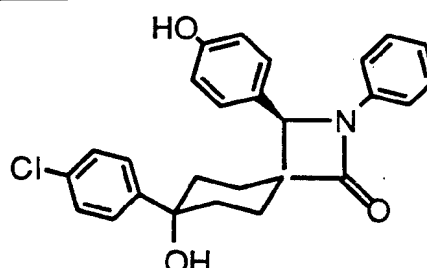
35C



mp=94-96°C

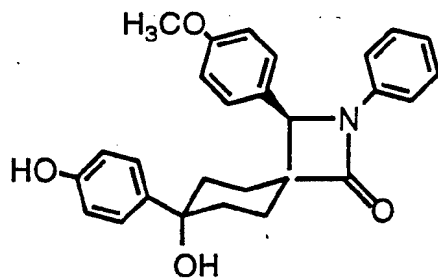
MS calcd: 427; obs: 427

35D

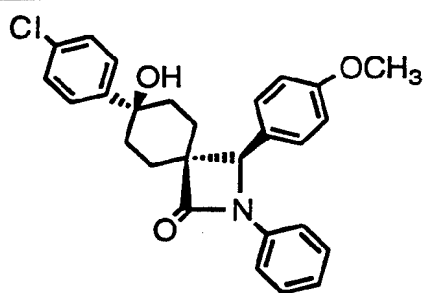
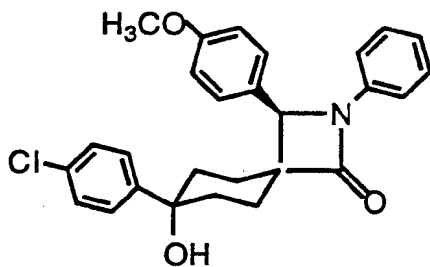


MS calcd: 433; obs: 416 (M-H₂O)

- 26 -

35EMS calcd: 429; obs: 412 (M-H₂O)**Examples 36, 36A, 36B, 37 and 38**

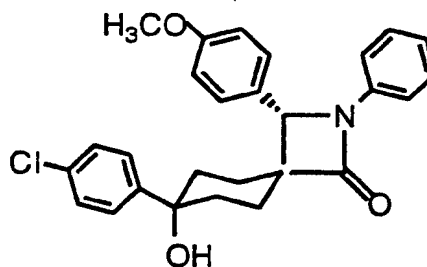
Using appropriate starting materials in a procedure similar to that described in Example 35, the following compounds are prepared:

36**36A**

mp = 100.0-103.0°C

 $[\alpha]_D^{20} = +55.9^\circ$ (CH₃OH)

single enantiomer

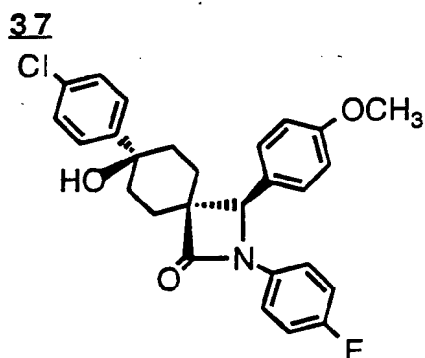
36B

mp = 60.0-65.0°C

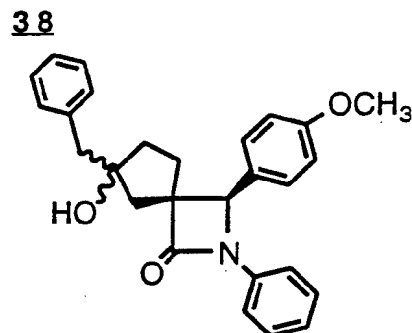
 $[\alpha]_D^{24.2} = -52.0^\circ$ (CH₃OH)

single enantiomer

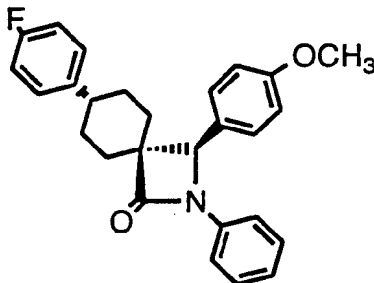
- 27 -



mp = 164.0-165.0°C



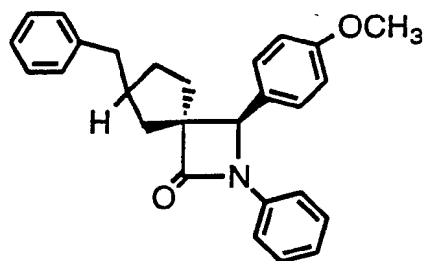
mp = 61.0-64.0°C

Examples 39, 40, 40A,

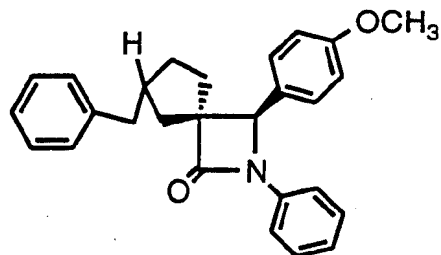
- STEP 1: Add p-TsOH (0.08 g) to a solution of the product of Example 35 (0.5 g) and stir at 60° C over 4A sieves for 3.5 hr. Filter the mixture through celite, wash with sat'd NaHCO₃, dry over Na₂SO₄, and evaporate to obtain 7-(4-fluorophenyl)-7-hydroxy-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.5]non-6-en-1-one, which can be used in STEP 2 with or without purification by chromatography over silica gel.
- STEP 2: To a solution of the product of STEP 1, (0.415 g, 1 mmol) in CH₂Cl₂ (15 mL), add (tricyclohexylphosphine)-(1,5-cyclooctadiene)-(pyridine) Iridium(I) hexafluorophosphate (0.010 g, 0.05 mmol). Stir under one atm H₂ at room temperature for 52 hr. Filter the mixture through a bed of silica gel, eluting with CH₂Cl₂ to give 0.161 g of the title compound, mp=146-147° C. MS calcd: 415; obs: 415.

In a similar manner, except using 10% Pd/C as the hydrogenation catalyst, use the compound of Example 38 as the starting material to prepare the following compounds:

- 28 -

40

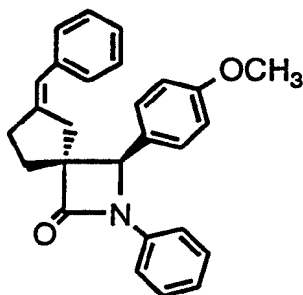
mp = 102-103°C

40A

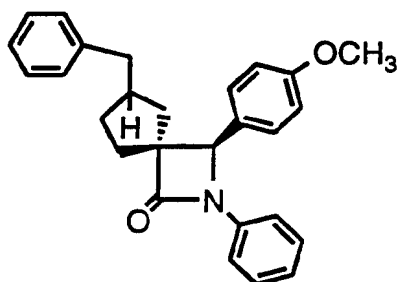
CI Mass Spectrum, M/z(intensity):
398 (100, M⁺), 279 (13), 211 (18).

Examples 41, 42 and 42A

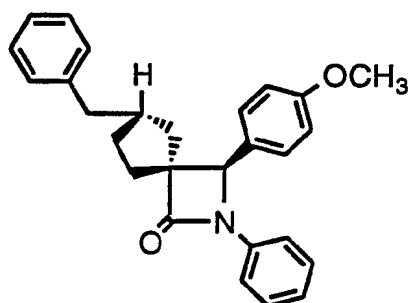
- 5 Use the product of Preparation 8 in the procedure of Example 35, followed by the procedure of Example 39, STEP 1, to obtain the compound of Example 41. Treat the compound of Example 41 using the procedure of Example 39, STEP 2, to obtain compounds of Examples 42 and 42A:

41

mp = 67.0-69.0°C

42

mp = 99-101°C

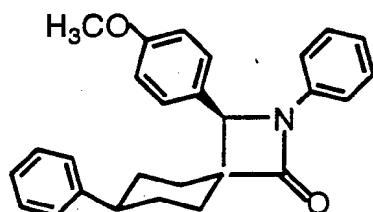
42A

mp = 102.0-103.0°C

- 29 -

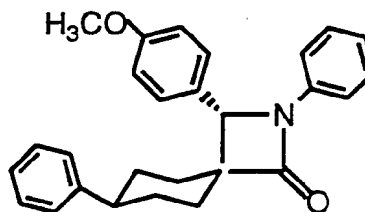
Examples 43A and 43B

Use the product of Preparation 7 in the procedure of Example 35, followed by the procedures of Example 39, STEP 1 and STEP 2, to obtain compounds of Examples 43A and 43B:

43A

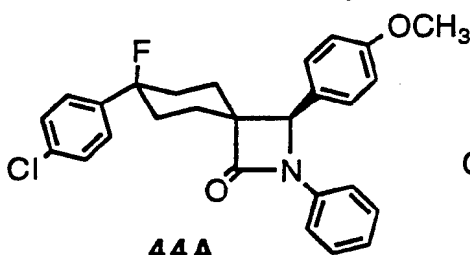
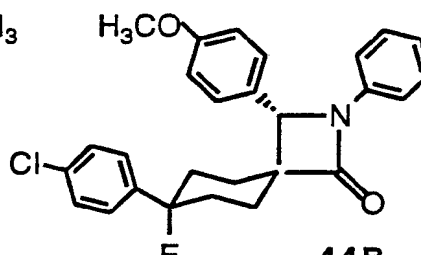
$$[\alpha]_D^{20} = +28.3^\circ \text{ (MeOH)}$$

single enantiomer

43B

single enantiomer

5

Examples 44A and 44B**44A****44B**

Dissolve the compound of Example 36 (0.31 g, 0.693 moles) in CH_2Cl_2 (7 mL) at -78°C and add dropwise, over 2-3 min., diethylamino-sulfur trifluoride (0.145 mL, 1.09 mmoles). Stir the mixture for 2 hr. at -78°C . Quench the mixture with ice-cold saturated NaHCO_3 and extract with CH_2Cl_2 (2x10 mL). Dry the combined organic layers over Na_2SO_4 and concentrate to an oil. Purify by flash chromatography on silica gel to obtain pure SYN diastereomer (0.146 mg) and impure ANTI diastereomer (0.72 mg). Purify the ANTI diastereomer by preparative TLC on a 20x20 cm silica gel plate, eluting with CH_2Cl_2 to obtain 0.026 g.

The following formulations exemplify some of the dosage forms of this invention. In each the term "active compound" designates a compound of formula I.

20

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EXAMPLE ATablets

| <u>No.</u> | <u>Ingredient</u> | <u>mg/tablet</u> | <u>mg/tablet</u> |
|------------|--|------------------|------------------|
| 1 | Active Compound | 100 | 500 |
| 2 | Lactose USP | 122 | 113 |
| 3 | Corn Starch, Food Grade, as a 10% paste in Purified Water | 30 | 40 |
| 4 | Corn Starch, Food Grade | 45 | 40 |
| 5 | Magnesium Stearate | 3 | 7 |
| | Total | 300 | 700 |

Method of Manufacture

- 5 Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the
- 10 mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE BCapsules

| <u>No.</u> | <u>Ingredient</u> | <u>mg/tablet</u> | <u>mg/tablet</u> |
|------------|-------------------------|------------------|------------------|
| 1 | Active Compound | 100 | 500 |
| 2 | Lactose USP | 106 | 123 |
| 3 | Corn Starch, Food Grade | 40 | 70 |
| 4 | Magnesium Stearate NF | 4 | 7 |
| | Total | 250 | 700 |

15 Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

20

Using the test procedures described above, the following in vivo data were obtained for the exemplified compounds. Data is reported

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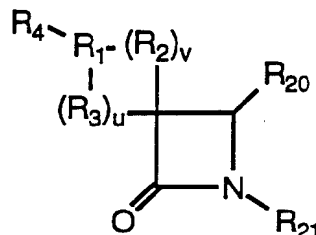
as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

| Ex. No. | % Change | Dose mpk | Ex. No. | % Change | Dose mpk | Ex. No. | % Change | Dose mpk |
|---------|----------|----------|---------|----------|----------|---------|----------|----------|
| 1 | -25 | 50 | 18 | 0 | 50 | 35A | 0 | 10 |
| 1A | -89 | 50 | 19 | -43 | 50 | 35B | -93 | 10 |
| 2 | -17 | 50 | 20 | 0 | 50 | 35C | -31 | 10 |
| 3 | -87 | 50 | 21 | -92 | 50 | 36 | -92 | 10 |
| 4 | 0 | 50 | 22 | -- | | 36A | -85 | 3 |
| 5 | -95 | 50 | 23 | -- | | | -62 | 1 |
| 6 | -26 | 50 | 24 | 0 | 50 | 36B | -18 | 3 |
| 7 | -64 | 50 | 25 | -43 | 50 | 37 | -91 | 10 |
| 8 | -17 | 50 | 26 | -97 | 25 | 38 | -21 | 10 |
| 9 | -46 | 50 | 27 | -32 | 25 | 39 | -- | |
| 10 | 0 | 50 | 28 | -65 | 50 | 40 | -90 | 50 |
| 11 | -25 | 50 | 29A | -9 | 50 | | -89 | 10 |
| 12 | -36 | 50 | 29B | 0 | 50 | 40A | -65 | 10 |
| 13 | -21 | 50 | 30A | -65 | 10 | 41 | -35 | 10 |
| 14 | -30 | 50 | 30B | -42 | 10 | 42 | -84 | 50 |
| 15 | 31 | 50 | 31 | -15 | 50 | 42A | 0 | 10 |
| 16 | 0 | 50 | 32 | -30 | 50 | 43A | -75 | 10 |
| 17A | -- | -- | 33 | 0 | 50 | | -55.5 | 3 |
| 17B | -- | -- | 34 | 0 | 50 | 43B | -- | |

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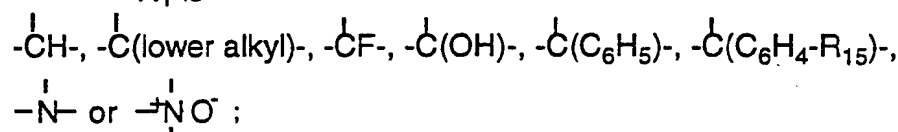
We claim:

1. A compound represented by the formula



- 5 or a pharmaceutically acceptable salt thereof, wherein:

R_1 is



- 10 R_2 and R_3 are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$, $-\text{C}(\text{di-lower alkyl})-$, $-\text{CH}=\text{CH}-$ and $-\text{C}(\text{lower alkyl})=\text{CH}-$; or R_1 together with an adjacent R_2 , or R_1 together with an adjacent R_3 , form a $-\text{CH}=\text{CH}-$ or a $-\text{CH}=\text{C}(\text{lower alkyl})-$ group;

- u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R_2 is $-\text{CH}=\text{CH}-$ or $-\text{C}(\text{lower alkyl})=\text{CH}-$, v is 1;
 15 provided that when R_3 is $-\text{CH}=\text{CH}-$ or $-\text{C}(\text{lower alkyl})=\text{CH}-$, u is 1;
 provided that when v is 2 or 3, the R_2 's can be the same or different; and
 provided that when u is 2 or 3, the R_3 's can be the same or different;

R_4 is $\text{B}-(\text{CH}_2)_m\text{C}(\text{O})-$, wherein m is 0, 1, 2, 3, 4 or 5;

$\text{B}-(\text{CH}_2)_q-$, wherein q is 0, 1, 2, 3, 4, 5 or 6;

- 20 $\text{B}-(\text{CH}_2)_e\text{-Z-(CH}_2)_r-$, wherein Z is $-\text{O}-$, $-\text{C}(\text{O})-$, phenylene, $-\text{N}(\text{R}_8)-$ or $-\text{S}(\text{O})_{0-2}-$, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6;

$\text{B}-(\text{C}_2\text{-C}_6 \text{ alkenylene})-$; $\text{B}'-(\text{C}_4\text{-C}_6 \text{ alkadienylene})-$;

- 25 $\text{B}-(\text{CH}_2)_t\text{-Z-(C}_2\text{-C}_6 \text{ alkenylene})-$, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

$\text{B}-(\text{CH}_2)_f\text{-V-(CH}_2)_g-$, wherein V is $\text{C}_3\text{-C}_6$ cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6;

- 30 $\text{B}-(\text{CH}_2)_t\text{-V-(C}_2\text{-C}_6 \text{ alkenylene})-$ or $\text{B}'-(\text{C}_2\text{-C}_6 \text{ alkenylene})\text{-V-(CH}_2)_t-$, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

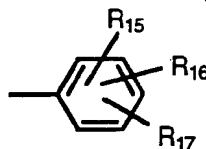
- 33 -

$B-(CH_2)_a-Z-(CH_2)_b-V-(CH_2)_d-$, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6;

$T-(CH_2)_s-$, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R_1 and R_4 together form the group $B-CH=C-\overset{|}{C}-$;

B is indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxyacetylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R7-benzyl, benzyloxy, R7-benzyloxy, phenoxy, R7-phenoxy, dioxolanyl, NO_2 , $-N(R_8)(R_9)$, $N(R_8)(R_9)$ -lower alkylene-, $N(R_8)(R_9)$ -lower alkylenyloxy-, OH, halogeno, $-CN$, $-N_3$, $-NHC(O)OR_{10}$, $-NHC(O)R_{10}$, $R_{11}O_2SNH-$, $(R_{11}O_2S)_2N-$, $-S(O)_2NH_2$, $-S(O)_{0-2}R_8$, tert-butyldimethylsilyloxymethyl, $-C(O)R_{12}$, $-COOR_{19}$, $-CON(R_8)(R_9)$, $-CH=CHC(O)R_{12}$, $-lower\ alkylene-C(O)R_{12}$, $R_{10}C(O)(lower\ alkylenyloxy)-$, $N(R_8)(R_9)C(O)(lower\ alkylenyloxy)-$ and $-CH_2-N\begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array}R_{13}$ for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, $-C(O)OR_{10}$, $-C(O)R_{10}$, OH, $N(R_8)(R_9)$ -lower alkylene-, $N(R_8)(R_9)$ -lower alkylenyloxy-, $-S(O)_2NH_2$ and 2-(trimethylsilyl)ethoxymethyl;

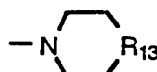
R7 is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, $-COOH$, NO_2 , $-N(R_8)(R_9)$, OH or halogeno;

R_8 and R_9 are independently H or lower alkyl;

R_{10} is lower alkyl, phenyl, R7-phenyl, benzyl or R7-benzyl;

R_{11} is OH, lower alkyl, phenyl, benzyl, R7-phenyl or R7-benzyl;

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R₁₂ is H, OH, alkoxy, phenoxy, benzyloxy, ,



-N(R₈)(R₉), lower alkyl, phenyl or R₇-phenyl;

R₁₃ is -O-, -CH₂-, -NH-, -N(lower alkyl)- or -NC(O)R₁₉;

R₁₅, R₁₆ and R₁₇ are independently selected from the group consisting of H and the groups defined for W; or R₁₅ is hydrogen and R₁₆ and R₁₇, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

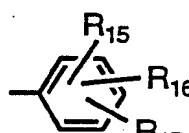
R₁₉ is H, lower alkyl, phenyl or phenyl lower alkyl; and

R₂₀ and R₂₁ are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

2. A compound of claim 1 wherein R₁ is  or .

3. A compound as claimed in claim 1 or claim 2 wherein R₂ and R₃ are each -CH₂- and the sum of u and v is 2, 3 or 4.

4. A compound as claimed in any one of claims 1 to 3 wherein

R₄ is B-(CH₂)_q or B-(CH₂)_e-Z-(CH₂)_r, wherein B is , q is 0-2, Z is -O-, e is 0, r is 0, R₁₆ is H, R₁₇ is H and R₁₅ is as defined in claim 1.

5. A compound as claimed in claim 4 wherein R₁₅ is H, OH, lower alkoxy or chloro.

6. A compound as claimed in any one of claims 1 to 5 wherein R₂₀ is phenyl or W-substituted phenyl, wherein W is as defined in claim 1.

7. A compound of claim 6 wherein R₂₀ is W-substituted phenyl and W is lower alkoxy, OH or -C(O)R₁₂, wherein R₁₂ is lower alkoxy.

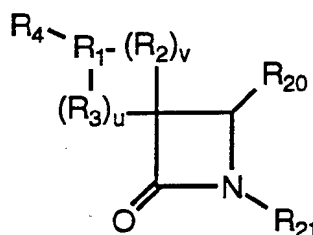
8. A compound as claimed in any one of claims 1 to 7 wherein R₂₁ is phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl,

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tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl, wherein W is lower alkyl, lower alkoxy, OH, halogeno, -N(R₈)(R₉), -NHC(O)OR₁₀, -NHC(O)R₁₀, NO₂, -CN, -N₃, -SH, -S(O)₀₋₂-(lower alkyl), -COOR₁₉, -CON(R₈)(R₉), -COR₁₂, phenoxy, benzyloxy, -OCF₃,

- 5 -CH=CHC(O)R₁₂ or tert-butyldimethylsilyloxy, and when W is 2 or 3, the groups can be the same or different.


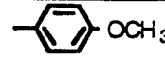

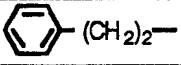
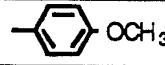

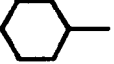
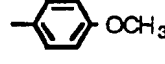



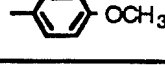


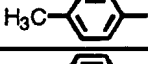
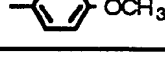


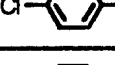




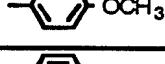



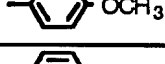


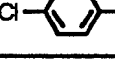
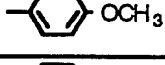



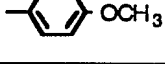


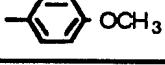

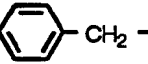
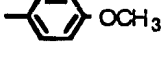

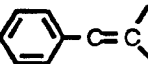
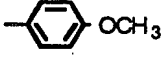

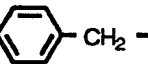
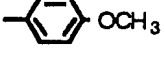


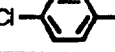
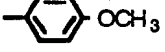

9. A compound of claim 1 represented by the formula



- 10 wherein R₁, R₂, R₃, R₄, R₂₀, R₂₁, u and v are as follows:

| | R ₁ | -(R ₂) _v - | -(R ₃) _u - | R ₄ | R ₂₀ | R ₂₁ |
|------|---------------------|------------------------------------|------------------------------------|----------------|-----------------|-----------------|
| i | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| ii | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| iii | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| iv | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| v | N | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| vi | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| vii | C(CH ₃) | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| viii | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| ix | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| x | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| xi | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| xii | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| xiii | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - | | | |
| xiv | | | -(CH ₂) ₂ - | | | |

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| | R ₁ | -(R ₂) _v - | -(R ₃) _u - | R ₄ | R ₂₀ | R ₂₁ |
|--------|---|------------------------------------|------------------------------------|--|---|---|
| xv | CH | -CH ₂ - | -CH ₂ - |  |  |  |
| xvi | CH | -CH ₂ - | -CH ₂ - |  |  |  |
| xvii | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  |
| xviii |  | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  |
| xix |  | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  |
| xx |  | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  |
| xxi |  | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  |
| xxii |  | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  |
| xxiii |  | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  |
| xxiv |  | -(CH ₂) ₂ - | -CH ₂ - |  |  |  |
| xxv | CH | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  |
| xxvi | CH | -(CH ₂) ₂ - | -CH ₂ - |  |  |  |
| xxvii | see R ₄ | -CH ₂ - | -(CH ₂) ₂ - | R ₁ and R ₄ together are  |  |  |
| xxviii | CH | -CH ₂ - | -(CH ₂) ₂ - |  |  |  |
| xxix |  | -(CH ₂) ₂ - | -(CH ₂) ₂ - |  |  |  |

10. A compound of claim 1 selected from the group consisting of:
 7-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.5]nonan-1-one;
 7-(4-chlorophenyl)-7-hydroxy-3-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.5]nonan-1-one;
 7-(4-chlorophenyl)-2-(4-fluorophenyl)-7-hydroxy-3-(4-methoxyphenyl)-2-azaspiro[3.5]nonan-1-one; and
 7-(4-chlorophenyl)-7-hydroxy-3-(4-hydroxyphenyl)-2-phenyl-2-azaspiro[3.5]nonan-1-one.

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11. A pharmaceutical composition comprising an effective amount of a compound as claimed in any one of claims 1 to 10 in a pharmaceutically acceptable carrier.
- 5 12. The use of a compound as claimed in any one of claims 1 to 10 for the manufacture of a medicament for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels.
- 10 13. A process for the preparation of a pharmaceutical composition as claimed in claim 12 which comprises admixing a compound as defined in claim 12 with a pharmaceutically acceptable carrier.
- 15 14. A method of lowering the serum cholesterol level, or treating or preventing atherosclerosis, in a mammal in need of such treatment comprising administering an effective amount of a compound of claim 1.
- 20 15. The use of a compound as claimed in any one of claims 1 to 10 for the manufacture of a medicament for the combined use with a cholesterol biosynthesis inhibitor in the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels.
- 25 16. The use of a cholesterol biosynthesis inhibitor for the manufacture of a medicament for the combined use with a compound as claimed in any one of claims 1 to 10 in the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels.
- 30 17. The use as claimed in claim 16, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors, squalene synthesis inhibitors and squalene epoxidase inhibitors.
- 35 18. The use as claimed in claim 17, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin, CI-981, L-659,699, squalastatin 1 and NB-598.

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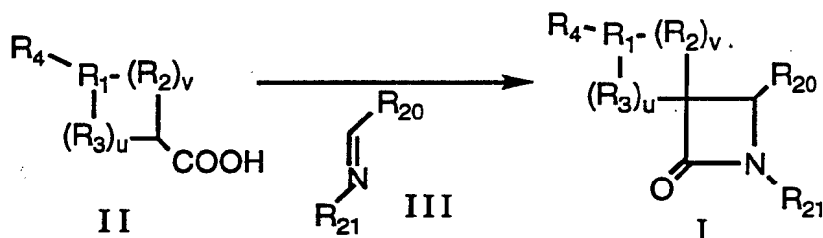
19. The use as claimed in claim 15, wherein the cholesterol biosynthesis inhibitor is as specified in claim 17 or claim 18.
20. A pharmaceutical composition for the treatment or prevention
5 of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising a compound as defined in any one of claims 1 to 10, a cholesterol biosynthesis inhibitor and a pharmaceutically acceptable carrier.
- 10 21. A pharmaceutical composition as claimed in claim 20, wherein the cholesterol biosynthesis inhibitor is as defined in claim 17 or claim 18.
22. A method for preparing a pharmaceutical composition as
15 claimed in claim 20 or claim 21 comprising admixing a cholesterol biosynthesis inhibitor and a compound as defined in any one of claims 1 to 10 with a pharmaceutically acceptable carrier.
23. A method as claimed in claim 22 comprising admixing a
20 cholesterol biosynthesis inhibitor as defined in claim 17 or claim 18, and a compound as defined in any one of claims 1 to 10 with a pharmaceutically acceptable carrier.
24. A kit comprising in separate containers in a single package
25 pharmaceutical compositions for use in combination to treat or prevent atherosclerosis or to reduce plasma cholesterol levels which comprises in one container an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier, and in a second container, an effective amount of a compound as defined in any one of claims 1 to 10 in
30 a pharmaceutically acceptable carrier.
25. A kit as claimed in claim 24 which comprises in one
container an effective amount of a cholesterol biosynthesis inhibitor as
defined in claim 17 or claim 18 in a pharmaceutically acceptable carrier,
35 and in a second container, an effective amount of a compound as defined in any one of claims 1 to 10 in a pharmaceutically acceptable carrier.

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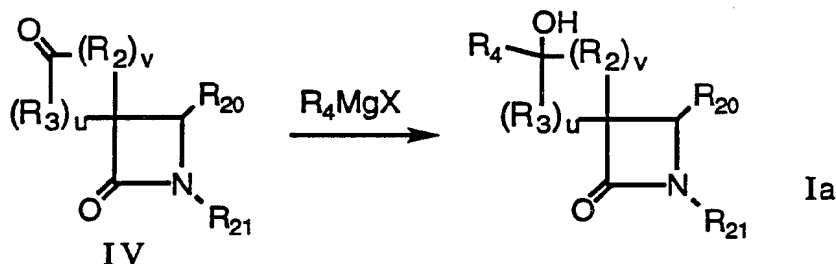
26. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising simultaneously or sequentially administering to a mammal in need of such treatment an effective amount of a cholesterol biosynthesis inhibitor and a compound as defined in any one of claims 1 to 10.

27. A method as claimed in claim 26, wherein the cholesterol biosynthesis inhibitor is as defined in claim 17 or claim 18.

28. A process for preparing a compound of claim 1 comprising Process A: Converting a carboxylic acid of formula II to the corresponding acid chloride, followed by reacting with an imine of formula III to obtain a compound of formula I

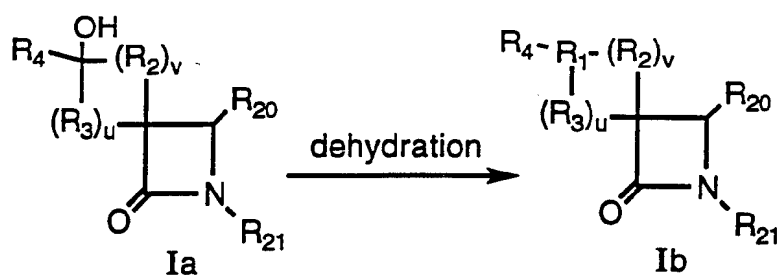


- wherein R_1 , R_2 , R_3 , R_4 , R_{20} , R_{21} , u and v are as defined in claim 1;
Process B: Reacting a keto-azetidinone of formula IV with a Grignard reagent of the formula R_4MgX , wherein R_4 is as defined in claim 1 and X is halogen, to obtain a carbinol of formula Ia



- wherein R_2 , R_3 , R_4 , R_{20} , R_{21} , u and v are as defined in claim 1 and R_1 is $-C(OH)-$;
Process C: Dehydrating a carbinol of formula Ia as defined in Process B to obtain an olefin of formula Ib

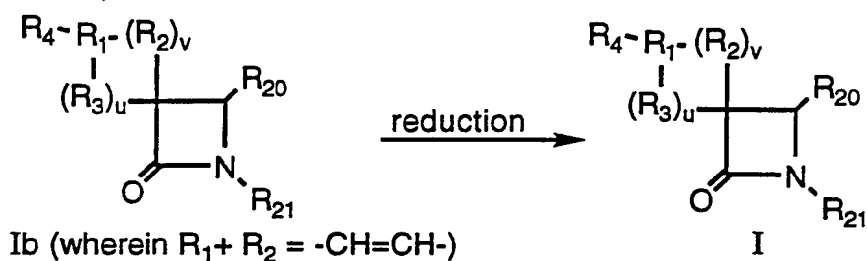
- 40 -



wherein $R_1 + R_2 = -CH=CH-$ and $R_2, R_3, R_4, R_{20}, R_{21}, u$ and v are as defined in claim 1; or

Process D: Reducing an olefin of formula Ib as defined in Process C to

- 5 obtain a compound of formula I



wherein $R_1, R_2, R_3, R_4, R_{20}, R_{21}, u$ and v are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/00421

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D205/12 C07D471/10 A61K31/395 //(C07D471/10,221:00,
205:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | TETRAHEDRON LETTERS vol. 33, no. 15, 1992, OXFORD GB pages 1993 - 1996 S. LE BLANC ET AL. 'New access to spiranic beta-lactams' see the whole document --- | 1,28 |
| A | CHEMICAL ABSTRACTS, vol. 90, no. 11, 1979, Columbus, Ohio, US; abstract no. 87242k, O. IWAQ 'Beta-lactams from schiff bases and ketene silylacetals' see abstract & JP,A,78 108 962 (SAGAMI CHEMICAL RESEARCH CENTER) 22 September 1978 --- | 1,28 |
| A | GB,A,1 356 145 (B.A.S.F. AG.) 12 June 1974 see page 3, line 106 - line 110; example 5 --- | 1,11,28 |
| -/- | | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

18 April 1994

Date of mailing of the international search report

26.04.94

Name and mailing address of the ISA

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Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/00421

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | CHEMICAL ABSTRACTS, vol. 97, no. 9, 1982, Columbus, Ohio, US; abstract no. 72198w, KHRISTOSKOVA S. ET AL. 'Asymmetric synthesis of 3-anilinopropanols and 2-azetidinones' see abstract & DOKL. BOLG. AKAD. NAUK vol. 34, no. 11, 1981, SOFIA pages 1509 - 1512 --- | 1,28 |
| A | CHEMICAL ABSTRACTS, vol. 74, no. 21, 1971, Columbus, Ohio, US; abstract no. 111819w, SIMOVA E. ET AL. 'Reactions of schiff bases with carboxylic acid derivatives in the presence of alkaline catalysts. Synthesis of 3,3-disubstituted 1,4-diphenyl-2-azetidinones.' see abstract & IZV. OTD. KHIM. NAUKI, BULG. AKAD. NAUK. vol. 3, no. 3, 1970, SOFIA pages 497 - 508 --- | 1,28 |
| A | US,A,4 692 515 (V.S. GEORGIEV ET AL.) 8 September 1987 see the whole document --- | 1,11,28 |
| A | US,A,5 130 425 (M.S. MALAMAS) 14 July 1992 see the whole document --- | 1,11,28 |
| P,A | EP,A,0 524 595 (SCHERING CORPORATION) 27 January 1993 see claims & WO,A,93 02048 (SCHERING CORPORATION) 4 February 1993 cited in the application ----- | 1,11,28 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/ 00421

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claims 14, 26, 27 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition."
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter: International Application No

PCT/US 94/00421

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|--|--|
| JP-A-78108962 | | NONE | |
| GB-A-1356145 | 12-06-74 | DE-A- 2048080 BE-A- 773173 CH-A- 546759 FR-A- 2108681 | 25-05-72 28-03-72 15-03-74 19-05-72 |
| US-A-4692515 | 08-09-87 | NONE | |
| US-A-5130425 | 14-07-92 | NONE | |
| EP-A-0524595 | 27-01-93 | AU-A- 2398092 CN-A- 1069024 WO-A- 9302048 | 23-02-93 17-02-93 04-02-93 |
| WO-A-9302048 | 04-02-93 | AU-A- 2398092 CN-A- 1069024 EP-A- 0524595 | 23-02-93 17-02-93 27-01-93 |